FDA VETERINARIAN

Center for Veterinary Medicine

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CVM Makes "Blue Bird" Medicated Feed Labels Available on Internet

The Center for Veterinary Medicine is making copies of approved "Blue Bird" Type B and Type C medicated feed labels available on the CVM Web site as a way to help ensure feed safety.

When a drug sponsor submits to CVM a New Animal Drug Application (NADA) for a Type A medicated article, which is product containing a drug that is used in feed, the NADA must include representative labels for Type B and/or Type C medicated feeds that are made from the Type A medicated article. The representative labels, called "Blue Bird Labels," are intended to guide medicated feed manufacturers in the preparation of accurate final product Type B and C medicated feed labels.

When submitting an application to the FDA for a medicated feed mill license to use certain Type A medicated articles, the feed mill's management commits to having the current approved Type B and/or Type C medicated feed labeling in its possession prior to receiving Type A medicated articles. The Food and Drug Administration had previously determined that feed mill managers would have the labeling in their possession if they could obtain such labeling via the Internet.

CVM determined that it could play a role in helping medicated feed mills have access to the most up-to-date and accurate Blue Bird labels by making those labels available on the CVM Web site.

CVM developed a Web-based repository of Blue Bird labels for use in preparation of medicated feeds containing either Category I or Category II drugs.

To get to the labels, go to the CVM page (*http://www.fda.gov/AnimalVeterinary/default.htm*) and click on the

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Dear Reader,

In an effort to make *FDA Veterinarian* more timely for you, we are converting it to a paperless publication after this issue. This is the last issue we will mail.

Future issues will be posted on the Food and Drug Administration's Center for Veterinary Web site *http://www.fda.gov/AnimalVeterinary/NewsEvents/FDAVeterinarianNewsletter/default.htm*.

Also, because it will be posted on the Web site, FDA Veterinarian will be available to you free of charge. We will no longer accept payment for subscriptions.

As always, if you have any questions or comments, please feel free to contact us at CVM through our home page. Please go to *http://www.fda.gov/AnimalVeterinary/default.htm*, where you will find all the contact information.

Jon F. Scheid,
Editor

The Commissioner's Fellowship Program: Training FDA Ambassadors

by Laura Alvey, Deputy Director, Communications Staff

In the fall of 2008, the Food and Drug Administration launched a Commissioner's Fellowship Program that provides an opportunity for health professionals and other scientists to receive training and experience within FDA.

The goal is to train a cadre of investigators intensively in the issues that relate to FDA regulatory science across devices, drugs (human and animal), biologics, foods (including animal feed), and cosmetics. Fellows train at FDA's new state-of-the-art campus in White Oak, MD, or at other FDA facilities.

The fellowship is designed as a 2-year program. Under the guidance of a preceptor (a senior FDA scientist committed to mentoring and selected by the Centers), Fellows explore in depth a specific aspect of FDA regulatory science. The experience can be

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In This Issue

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PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

…"Blue Bird" Medicated Feed Labels Available on Internet *(Continued)*

"Products" navigational button. After you get to the "Products" page, click on the "Drug Labels" navigational button. There, click on the "Blue Bird Labels" button. *http://www.fda.gov/AnimalVeterinary/Products/AnimalFoodFeeds/MedicatedFeed/BlueBirdLabels/default.htm*). The labels are sorted by species, and then by product active ingredient.

The repository is incomplete at this time. It includes only a fraction of all currently approved Blue Bird labels. However, CVM intends to continue expanding the repository as more labels become available.

The Commissioner's Fellowship Program *(Continued)*

in a wet lab, with a clinical review or evaluation team, in biostatistics, informatics, epidemiology, risk analysis, or another aspect of FDA science.

Every regulatory decision made by FDA is based on science. Fellows explore the nature of these decisions with their preceptors and learn the scientific foundations upon which these decisions are made.

The coursework is designed to provide an in-depth review of the sciences behind regulatory review, encompassing the activities of FDA across foods, drugs, devices, and cosmetics. Coursework during the two years includes public policy, FDA law, leadership skills, epidemiology, clinical trials, statistics as well as devices and radiological health.

Overview

There is a wide range of training experiences at FDA open to those who wish to acquire specific experiences in the sciences of FDA regulation. These include short-term FDA training experiences as well as longer experiences in laboratories, epidemiological and behavioral areas, and in product review.

The FDA Commissioner's Fellowship Program is not meant to replace the current fellowships and other educational experiences at FDA. The new program provides exposure to FDA law, policy, the Federal government budgeting process, networking and leadership skills, international activities, communication with the public and press, biostatistics, epidemiology, clinical trial design, risk assessment, and risk management as well as extensive case-based learning. In conjunction with this didactic training, Fellows, with the guidance of their preceptors, engage in a carefully designed and articulated FDA regulatory science project.

The intent of the Fellowship is to identify and train highly accomplished individuals who will be FDA ambassadors throughout their scientific careers. FDA anticipates that some of these Fellows would remain at FDA after their Fellowships. While others would seek jobs in industry where the knowledge and perspectives they gained would prove invaluable for their subsequent interactions with FDA and their contributions to regulatory science.

The FDA Commissioner's Fellowship Program is designed for highly motivated and creative physicians, microbiologists, chemists, statisticians, physicists, physiologists, pharmacists, pharmacologists, engineers, food scientists, nutritionists, veterinarians, social scientists, epidemiologists, and other scientific professionals.

In the medical, biological, mathematical risk management and statistical sciences, applicants are expected to have an M.D., D.V.M., Pharm.D, or Ph.D. degree or equivalent; for engineering applicants, a Bachelor's degree is required.

FDA Approves First Drug to Treat Hyperthyroidism in Cats

by Melanie McLean, D.V.M., Communications Staff

"My 12-year-old cat 'Bear' has been having diarrhea off and on for awhile now. He's always hungry, but he's getting skinnier. He never seems full even though I'm feeding him five meals a day. I see him at his water bowl a lot, too." A small animal veterinarian hears variations of Bear's owner's story often, and feline hyperthyroidism is always on the top of the rule-out list.

In the past, when hyperthyroidism was the diagnosis, there was no drug approved specifically for cats to treat this disease. Now that has changed.

In May 2009, the Food and Drug Administration approved FELIMAZOLE (methimazole). FELIMAZOLE, manufactured by Dechra, Ltd., in Staffordshire, United Kingdom, is the first, and currently only, FDA-approved drug for the treatment of hyperthyroidism in cats.

Also called thyrotoxicosis, hyperthyroidism is an endocrine disease that

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FDA Approves Drug to Treat Cancer in Dogs

by Melanie McLean, D.V.M., Communications Staff

Being told your dog has skin cancer is always scary. However, if it's a type of skin cancer called a cutaneous mast cell tumor (MCT), it may not be so scary anymore.

In May 2009, the Food and Drug Administration approved PALLADIA (toceranib phosphate) to treat canine cutaneous MCTs. PALLADIA, manufactured by Pharmacia & Upjohn Company, a Division of Pfizer, Inc., New York, NY, is the first drug approved specifically for the treatment of cancer in dogs.

MCTs are the most common skin cancer in dogs, accounting for about 20 percent of the cases of canine skin tumors. MCTs can occur anywhere on the dog's body, and they have no "typical" appearance.

Many cancers, including MCTs, are classified by a histologic grade based on the degree of differentiation of the cancer cells. The term differentiation means how much the cancer cells resemble or differ from the normal cells of the same tissue type. Cancer cells that closely resemble the normal cells are called well differentiated. Poorly differentiated or undifferentiated cancer cells may have a primitive or bizarre appearance. A well differentiated cancer typically behaves less aggressively than a poorly differentiated one; that is, it grows more slowly and is less likely to be invasive or metastasize (spread to other parts of the body).

The three-tiered Patnaik system is used to grade MCTs. Grade I (low grade) MCTs are well differentiated, Grade II (intermediate grade) are moderately differentiated, and Grade III (high grade) are poorly differentiated or undifferentiated. It is important to know the grade of the MCT when discussing a dog's prognosis. A dog with a Grade I or II MCT has a better prognosis for long-term survival than a dog with a Grade III MCT. The best way to determine the grade of a MCT is with a biopsy.

Many cancers, including MCTs, are also classified by a clinical stage based on the degree of metastasis. There are three components to staging: the size of the primary tumor, the spread to regional lymph nodes, and the presence or absence of metastases (secondary tumors in other parts of the body). There are five stages (Stage 0 to Stage IV) of the generally recognized clinical staging system for MCTs. In most cases, the higher the stage, the poorer the prognosis. MCTs can spread to the liver,

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… Hyperthyroidism in Cats *(Continued)*

results from the over-production of thyroid hormones by the thyroid gland. FELIMAZOLE works by blocking this over-production.

Hyperthyroidism is the most common endocrine disease of cats older than 8 years of age. In almost 99 percent of the cases, it is caused by a benign tumor of the thyroid gland. The butterfly-shaped thyroid gland is located in the neck, with one lobe on each side. It plays an important role in regulating the body's "engine," or metabolic rate. When the thyroid gland produces an excessive amount of thyroid hormones, it causes the cat's "engine" to run at an abnormally high speed. Almost all of the cat's organs are affected by this high metabolic rate.

The most common clinical sign of hyperthyroidism in cats is weight loss despite an increased appetite. Other common clinical signs include vomiting, diarrhea, hyperactivity, drinking and urinating more than normal, and an unkempt hair coat. Because the disease develops gradually, many cat owners miss the early signs of hyperthyroidism, causing a delay in diagnosis and treatment.

Hyperthyroidism often leads to high blood pressure (hypertension) and heart disease. Hypertension is a consequence of the increased pumping pressure of the heart. In some cats, the blood pressure becomes so high that retinal hemorrhage or detachment occurs, resulting in sudden blindness. Heart disease develops because the heart must pump faster and more forcefully to meet the body's increased metabolic demands. To compensate for this increased workload, the muscles of the heart thicken, causing heart enlargement and eventual heart failure. The mortality rate of untreated hyperthyroidism is almost 100 percent.

A veterinarian may suspect that a cat has hyperthyroidism by the clinical signs described by its owner and by feeling the enlarged thyroid gland in its neck. The most common way to confirm the diagnosis is a blood test that measures the level of one of the thyroid hormones called thyroxine (T4). This is referred to as the cat's total T4 (TT4) concentration.

One treatment option for hyperthyroidism is oral medication, which can be given life-long or to stabilize the cat prior to other treatment options, such as radioactive iodine therapy or surgery. Until FELIMAZOLE, there was no approved oral medication available for veterinary use in the United States. For years, veterinarians have used the human-approved form of methimazole in an extralabel ("off label") manner in cats. But now there is FELIMAZOLE, a veterinary-approved form of methimazole. Unlike the human methimazole products, the effectiveness and safety of FELIMAZOLE have been evaluated specifically in cats and the product label provides dosing and safety information specific to the cat.

Regulatory Activities: Warning Letters March–August 2009

WARNING LETTER TO: Glen A. Dykstra, owner, Dyna-Moo Dairy, LLC: Everson, WA

Reason for Letter: Violative drug residues, improper extralabel drug use

Date: March 24, 2009

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm131719.htm

On or about July 14, 2008, the owner sold a dairy cow for slaughter, which was later found by the U.S. Department of Agriculture's Food Safety and Inspection Service (USDA/FSIS) to have violative residues of the drug penicillin in its kidney tissue. Thus, food from this cow was adulterated within the meaning of the Federal Food, Drug, and Cosmetic Act (FFDCA).

Further investigation by the Food and Drug Administration found that the animals are housed at this operation under inadequate conditions, whereby medicated animals with potentially harmful drug residues are likely to enter the food supply. Thus, food from these animals is adulterated within the meaning of the FFDCA.

The FDA investigation also found that penicillin was used in an extralabel manner and not under the supervision of a licensed veterinarian. Use of the drug in this manner caused it be unsafe and adulterated within the meaning of the FFDCA and resulted in an illegal drug residue.

WARNING LETTER TO: Richard L. and Donald P. Templeton, owners, Templeton Dairy, LLC: Evansville, WI

Reason for Letter: Violative drug residues

Date: March 27, 2009

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm131716.htm

On or about September 25, 2008, the owners consigned a dairy cow for slaughter, which was later found by the USDA/FSIS to have violative residues of the drug ampicillin in its kidney tissue. Thus, food from this cow was adulterated within the meaning of the FFDCA.

Further investigation by FDA found that the animals are housed at this operation under inadequate conditions, whereby medicated animals with potentially harmful drug residues are likely to enter the food supply. Thus, food from these animals is adulterated within the meaning of the FFDCA.

WARNING LETTER TO: Lyle J. Borkholder, owner, Borkholder Farms: Nappanee, IN

Reason for Letter: Violative drug residues, improper extralabel drug use

Date: April 22, 2009

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm162793.htm

On or about July 19, 2008, the owner sold a dairy cow for slaughter, which was later found by the USDA/FSIS to have violative residues of the drug sulfadimethoxine in its liver and muscle tissues. Also, on or about September 17, 2008, the owner sold another dairy cow for slaughter, which was later found by the USDA/FSIS to have violative residues of the sulfadimethoxine in its liver tissue.

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… Drug to Treat Cancer in Dogs *(Continued)*

spleen, bone marrow, and blood, as well as other sites in the body. Usually, a MCT spreads first to the draining (regional) lymph node. Evaluation of the regional lymph nodes is the most important part in determining the clinical stage of a MCT.

Surgery, radiation therapy, and chemotherapy are available treatment options for MCTs in dogs. Surgery is the treatment of choice. Radiation therapy and chemotherapy are commonly performed after surgery, if necessary. Until the recent approval of PALLADIA, all chemotherapeutic drugs used to treat MCTs in dogs were developed for use in humans and prescribed by veterinarians in an extralabel ("off label") manner.

PALLADIA is approved for the treatment of Patnaik Grade II or III, recurrent, cutaneous MCTs with or without regional lymph node involvement in dogs. It is a tyrosine kinase inhibitor and works by killing the cancer cells and cutting off their blood supply.

CVM Uses Seven-Step Process to Evaluate Safety, Effectiveness of GE Animals

by Melanie McLean, D.V.M., Communications Staff

The Food and Drug Administration's Center for Veterinary Medicine evaluates genetically engineered (GE) animals through a rigorous, seven-step review process that looks at the safety of the introduced trait to the animals themselves, to any food derived from the animals, and to the environment. The process uses the same requirements for safety and effectiveness that are used for the review of any new animal drug.

A GE animal is an animal that contains altered or additional genetic material (DNA). This altered or additional piece of DNA, called recombinant DNA (rDNA or the rDNA construct) is introduced into the animal to produce a desirable trait, such as the ability to resist disease, produce a pharmaceutical for human use, or grow faster.

In the Federal Food, Drug, and Cosmetic Act (FFDCA), the term "drug" includes "articles (other than food) intended to affect the structure or any function of the body of man or other animals." The rDNA construct (also called "the article") that is introduced into the animal meets this legal definition of a drug because it is intended to affect the structure or function of the GE animal. So the GE animal itself is not a drug, but CVM has the authority to regulate GE animals carrying the rDNA construct under the new animal drug provisions of the FFDCA.

Products derived from GE animals are regulated by the appropriate FDA center. For example, human pharmaceuticals produced by GE animals are regulated by the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research, depending on whether the pharmaceutical is a drug or a biologic.

Conventional laws apply

CVM developed its approach for regulating GE animals using the existing laws. For example, the FFDCA requires that all new animal drugs be the subject of a New Animal Drug Application (NADA). To be approved, the NADA must demonstrate the safety and effectiveness of the drug for its intended use, so any approval for an rDNA construct in a GE animal must be shown to be safe and effective.

On January 15, 2009, CVM issued the final Guidance for Industry (GFI) #187: Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Constructs (this guidance can be found at *http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm113903.pdf*). GFI #187 provides specific recommendations to help developers of GE animals meet the statutory and regulatory requirements of the NADA process. GFI #187 states that although the FDA intends to regulate non-heritable rDNA constructs (which are not passed on to offspring) in much the same way as heritable rDNA constructs, its primary focus is on heritable rDNA constructs that are passed from generation to generation.

CVM developed a cumulative, weight-of-evidence, risk-based approach for reviewing data in support of an application for approval of an rDNA construct in a GE animal containing an rDNA construct. The approach is cumulative because as each step in the review process is completed, the knowledge gained "forms the basis and context for the evaluation of subsequent steps," explained Dr. Jeff Jones, a Veterinary Medical Officer in the Animal Biotechnology Group at CVM. He described the weight-of-evidence component as "looking at all the information as a whole to make our decision," and said that the risk-based component "focuses on where potential harm may arise from the use of this [GE] technology."

The review process for a GE animal carrying an rDNA construct is "a big picture approach," explained Dr. Barry Hooberman, a Regulatory Policy Analyst in CVM's Office of Surveillance and Compliance. "We want to make sure that the questions we ask are appropriate for the product under review; in other words, scaling the risk questions to the product at hand."

Seven-step review

The first three steps of the seven-step review process concentrate on defining and characterizing the rDNA construct and its integration into the resulting GE animal. The next three steps focus more on whether the GE animal poses any risks to humans, to

(Continued, next page)

CVM Uses Seven-Step Process... *(Continued)*

its own health, or to the environment. The last step of the process addresses effectiveness and validates the claim proposed in the first step.

Step 1: Product identification/definition: The first step asks the question, "What is it, and what is its intended use?" The product identification is a broad statement that describes the rDNA construct and the GE animal containing it and also defines the proposed claim for or intended use of the rDNA construct.

Step 2: Molecular characterization of the construct: This step asks the question, "Will the rDNA construct itself or the way it is assembled pose any risks?" To determine if any risks exist, CVM evaluates whether the rDNA construct contains any DNA sequences that may be potential hazards to the GE animal itself, to humans or other animals consuming food from that animal, or to the environment.

Step 3: Molecular characterization of the GE animal lineage: This step asks the questions, "Does the introduction of the rDNA construct into the animal pose any risks?" and, "Is the rDNA construct stable over several generations of GE animals?" To answer the first question, CVM makes sure that the DNA sequences in the rDNA construct have not rearranged during the introduction process and that the insertion sites are identified. To determine the stability of the rDNA construct, CVM evaluates whether it is maintained in the animal in the same place, with the same number of copies, and with the same general structure over the life of the animal and over several generations of the animal's offspring.

Step 4: Phenotypic characterization of the GE animal: The phenotype of an animal is its outward appearance and is determined by the interplay of the animal's genes and environmental influences. Step 4 evaluates the safety of the rDNA construct on the phenotype of the GE animal. It asks the questions, "How does the animal look and act?" and, "Is the animal healthy?" CVM evaluates whether the rDNA construct poses any direct or indirect risks to the GE animal by reviewing comprehensive data on its health, including veterinary and treatment records, growth rates, reproductive function, and behavior. Data on the physiological status of the GE animal, including clinical chemistry, hematology, histopathology, and post-mortem results, are also reviewed.

Step 5: Genotypic and phenotypic durability assessment: This step describes a plan to ensure that the introduced trait will remain the same over time and continue to have the same effect. It asks the question, "Are the genotype and phenotype changing over time?" To demonstrate genotypic durability, data are evaluated to show that the rDNA construct is stably inherited and there is a reasonable expectation that it will continue to be stably inherited. To demonstrate phenotypic durability, the intended trait should be consistently and predictably expressed over multiple generations. CVM recommends that data on inheritance be collected from at least two non-contiguous generations (e.g., second and fourth generations). The durability plan also describes a detection method for determining if a given animal continues to contain the rDNA construct and if its expression has significantly changed over time. In addition, the durability plan describes what actions will be taken if any detected changes are anticipated to affect the safety and effectiveness of the rDNA construct in the GE animal.

Step 6: The food/feed safety and environmental safety assessments: This step includes two safety assessments. The first focuses on the safety of food or feed derived from a GE animal for consumption by humans or other animals. The second addresses the environmental component of the NADA.

The food/feed safety assessment asks the question, "What is the risk of direct or indirect toxicity associated with humans or other animals consuming edible products derived from the GE animal?" An example of a direct toxicity is allergenicity, or, simply put, if the edible product is a known food allergen in humans. Indirect toxicity may occur if the consumption of the edible product creates an unintended risk to the human or animal consuming it. If a GE animal is not intended to produce an edible product, there should be evidence to demonstrate that neither the animal nor any products derived from it will enter the food supply. In all cases, the food/feed safety assessment process includes developing and validating the method used to detect the rDNA construct in food and feed materials derived from GE animals.

The environmental safety assessment asks the question, "What are the direct or indirect effects from the introduction of the GE animal into the environment?" In compliance with the requirements of the National Environmental Policy Act, CVM assesses the potential environmental impact related to the use and disposal of the GE animal and its final product.

Step 7: Effectiveness/claim validation: This step demonstrates that the GE animal fulfilled the product definition stated in the beginning of the NADA review process. It asks the question, "Does the GE animal meet the product definition in Step 1?" For example, for a disease resistance claim, the GE animal should

(Continued, next page)

CVM Uses Seven-Step Process... *(Continued)*

FDA Approves First Human Biologic Produced by GE Animals

When people think of life-saving products approved by the Food and Drug Administration for use in human medicine, goats don't usually come to mind. But for a person affected by a rare clotting disorder called hereditary antithrombin (AT) deficiency, a group of goats living in Framingham, MA, may be a true life saver.

These goats are genetically engineered (GE) to produce human AT in their milk. After the human AT is purified from the goats' milk, the biological product, called ATryn, is used as an anticoagulant to prevent blood clots in patients with hereditary AT deficiency. People living with this disorder are at high risk of developing life-threatening blood clots, especially during pregnancy, surgery, or prolonged bed rest. The approval of ATryn provides patients with hereditary AT deficiency a new and reliable source of the anticoagulant.

The FDA approved ATryn on February 6, 2009, and it is the first approval of a human biological product produced by GE animals in the United States. In a joint effort between the FDA's Center for Biologics Evaluation and Research (CBER) and Center for Veterinary Medicine, the manufacturer of ATryn, GTC Biotherapeutics, Inc., in Framingham, MA, received two approvals: one from CBER for the human anticoagulant and one from CVM for the recombinant DNA (rDNA) construct in the GE goats.

CBER approved the human anticoagulant based on its safety and effectiveness in humans, while CVM approved the rDNA construct based on its safety and ability to consistently produce the human AT over seven generations of the GE goats. The rDNA construct is a segment of DNA that, when introduced and expressed in the goats, gives them the ability to produce the human anticoagulant in their milk.

CVM determined that the introduction and expression of the rDNA construct in the goats do not pose any health risk to the animals and that the GE goats do not significantly impact the environment.

Neither the GE goats nor any products derived from them are intended to be consumed as food, and CVM made sure that there are adequate procedures in place to prevent the GE goats and their products from entering the food supply. In addition, CVM validated GTC's method for identifying the rDNA construct in both animals and their products and concurred with GTC's durability plan for post-approval monitoring of the rDNA construct and its expression.

indeed be resistant to that disease. For a non-food product claim, such as a pharmaceutical for human use, the GE animal should indeed produce that product. In addition, this step evaluates the impact on public health if the GE animal does not meet the proposed claim.

Uses for GE animals

CVM applied this cumulative, weight-of-evidence, risk-based approach to the review of GE goats carrying an rDNA construct that gives the goats the ability to produce human antithrombin (AT) in their milk. After the human AT is purified from the goats' milk, the biological product, called ATryn, is used as an anticoagulant to prevent blood clots in patients with a rare clotting disorder called hereditary AT deficiency. CVM reviewed and approved the rDNA construct in the GE goats, and the FDA's Center for Biologics Evaluation and Research reviewed and approved the human anticoagulant produced by the goats. It is the FDA's first approval of a human biological product made by GE animals.

Goats producing human AT in their milk are an example of the use of GE animals for biopharm purposes. Biopharm means using GE animals to produce substances (e.g., in their milk or blood) for use as pharmaceuticals in human or veterinary medicine. Currently, most GE animals are being developed for these purposes. Another group of GE animals under development are to be used as sources of scarce cells, tissues, and organs for transplantation into humans (xenotransplantation). Other GE animals are intended for food and may be disease resistant, have improved nutritional or growth characteristics, or have less of an environmental impact during rearing. For those allergic cat lovers, genetic engineering may also find a way to develop a hypoallergenic feline.

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Pain Measurement Techniques for Food-Producing Animals Could Lead to Pain Control Drugs

by Carmen Stamper, D.V.M., Communications Staff, with contributions from Sanja Modric, Ph.D., Office of New Animal Drug Evaluation

Pain relief in animals currently is a hot topic in veterinary medicine.

Companion animal medicine, in particular, is leading the way regarding patient pain management. Drug sponsors have realized the public's demand for pet analgesics, and, as a result, new non-steroidal anti-inflammatory drugs (NSAIDs) have been developed and approved for use in providing pain control for conditions such as osteoarthritis in dogs and postoperative pain and inflammation in dogs and cats.

In contrast, no drugs are approved for food animal analgesia in the United States. A major reason for the lack of approved food animal analgesics is that there are no validated methods for evaluating pain responses in food animals. For an analgesic to be FDA-approved, it has to undergo studies showing it is safe and effective. However, because no valid methods to measure food animal pain are available, the studies needed to show the analgesic actually controls pain are difficult to design.

Many groups around the world are working to identify and develop objective methods for measuring pain in cattle. Once these methods are developed and validated, they can be used in the development and approval of safe and effective analgesic drugs for use during painful cattle husbandry practices and to control pain associated with various painful conditions commonly encountered in cattle management (for example, lameness).[1]

What is pain?

Pain is defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." The IASP adds, "The inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment." This is an important point—especially when discussing pain in animals, and even more so in food-producing animals, such as cattle. Animals can visibly communicate their pain to us only through physical signs; however, stoic animals, such as cattle in general, may have subtle signs that can be missed.

Many research groups around the world are attempting to solve the great mysteries of pain in both humans and other animals; how pain is transmitted, how it is processed, and how we control it.

Pain is a complex phenomenon. It involves many nerve cells, many types of nerve chemicals, and many different nerve cell receptors to which the nerve chemicals bind in order to continue a pain signal's trip to the spinal cord and brain.[2]

Not only is pain complex from the standpoint of transmission, processing, and control, it is also complex in that there are different types of pain that have been identified based on cause or pathophysiology, the most important of which, for purposes of this discussion, are acute pain and chronic pain. Because the causes, transmission, and methods of processing of pain are complex issues, it is understandable that pain management and pain control are complicated and difficult.

Acute pain: Acute pain is a protective mechanism that can be defined as "the everyday experience of discomfort that occurs in response to a simple insult or injury." [3] Acute pain makes us notice an injury, move away from the danger that caused the injury, and then take care of the injury; thus, it is generally short-lived

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CVM Uses Seven-Step Process... *(Continued)*

Conclusion

The review of an rDNA construct in a GE animal is "a rigorous science- and risk-based process that asks questions that are appropriate for this technology," said Dr. Jones.

Dr. Hooberman added, "We try to be sure that we're asking and answering the right questions."

As more GE animals are being developed, CVM expects more NADAs for GE animals carrying rDNA constructs to be submitted. CVM encourages developers of GE animals to discuss the NADA requirements with CVM early in the development process.

Pain Measurement Techniques . . . *(Continued)*

pain. Pain associated with more severe trauma, like surgery, begins as acute pain but can become chronic with prolonged inflammation.[4]

Chronic pain: Chronic pain is a persistent kind of pain that may or may not be associated with injury, but is generally associated with inflammation, changes to nerve cells, and hyperexcitability of the nerve cells in the spinal cord and brain.[5] This hyperexcitability phenomenon, or "wind up," is a physiologic increase in sensitization of excitable nerve cells. Because the brain and spinal cord are now wound up to detect pain, they are hypersensitive to future painful stimuli—thus, something normally mildly painful becomes very painful after repeated physical insults. (How many times have you consecutively banged your "funny bone" and found that each new hit was more painful than the last?) In addition, the wind-up phenomenon changes in the spinal cord and brain make pain resistant to treatment with analgesics.[6]

Prolonged inflammation caused by damaged tissue helps perpetuate the wind-up phenomenon and plays a large role in chronic pain.[7] Preventing the wind-up phenomenon is an important human pre-surgery consideration; studies have shown that if analgesic or anti-inflammatory drugs are given to a patient prior to surgery, less analgesic or anti-inflammatory drugs are needed to control pain after surgery.[8] So, preemptively controlling pain and inflammation associated with a surgery prior to the surgery itself may decrease the development of chronic pain. Additionally, use of surgical procedures that minimize inflammation may decrease the likelihood of chronic pain development.

Problems in detecting pain

Recognizing pain in cattle is an important step toward alleviating their pain and improving their well-being. Unfortunately, pain recognition in cattle is difficult due to their evolution as prey animals. Cattle (like other prey animals) learned to hide signs of pain and weakness in order to prevent becoming a predator's next meal. This self-preservation instinct, a help in the wild, can hinder veterinarians and producers trying to recognize and alleviate pain in their animals.

Signs commonly associated with pain in cattle include: vocalization (grunting or bellowing), abnormal standing posture, teeth grinding, tail swishing, changed facial expressions, decreased body weight or milk production, reluctance to move, decreased appetite, decreased grazing, kicking or stamping of feet, restlessness, head turning, limping, and depression.[9,10,11]

In 2006, Huxley and Whay published an eye-opening article regarding cattle practitioners and their attitudes toward pain and use of pain drugs in cattle.[12] The authors sent a survey to nearly 2,400 cattle practitioners working in the UK and received 615 evaluable responses. Practitioners indicated that the most painful procedure for adult cattle was claw amputation and for calves was lower leg fracture repair and umbilical hernia repair. Surprising differences were found in assigned pain scores between women and men veterinarians and also among graduates from different decades: women and recent graduates generally gave higher scores, meaning higher levels of pain, for most conditions listed in the survey. Interestingly, although analgesics were widely used among practitioners, those who routinely used analgesics generally assigned higher pain scores to procedures than those who did not. Thus, the ability to recognize pain appears to drive the use of analgesics in practice. Based on the survey data, the authors recommended that current information regarding pain recognition and analgesic use in cattle be disseminated to UK cattle practitioners to ensure appropriate analgesia for cattle.[13]

In 2007, Dr. Hans Coetzee, BVSc, Ph.D., CertCHP, MRCVS, DACVCP, Assistant Professor of Clinical Pharmacology at Kansas State University College of Veterinary Medicine, and a group he organized conducted a small Web-based survey of U.S. bovine practitioners. Interestingly, only one in five respondents reported using analgesics at the time of castration. Why? The respondents stated they were concerned about using unapproved drugs in an extralabel manner in cattle due to requirements for careful calculation and observation of withdrawal times in treated animals. (Extralabel drug use refers to the use of a drug in a manner that is not in accordance with the approved labeling. Extralabel use of a drug can include use of the drug for indications, species, dosage levels, routes of administration, or withdrawal times not listed in the approved labeling.[14] A withdrawal time is the interval between the time of the last administration of a drug and the time when the treated animal can be safely slaughtered for food or its milk can be safely consumed.[15])

CVM's interest

Unlike the situation in small-animal medicine, there are no validated science-based pain assessment tools for use in cattle. This lack of validated pain assessment tools provides a significant hurdle in the development of analgesics for cattle.

CVM's Guidance for Industry #123 ("Development of Target Animal Safety and Effectiveness Data to

(Continued, next page)

Pain Measurement Techniques . . . *(Continued)*

Support Approval of Non-Steroidal Anti-Inflammatory Drugs (NSAIDS) for Use in Animals") discusses development and approval of NSAIDs for animals and encourages the use of validated methods of pain assessment in the target species. CVM recognizes the current limitations of this recommendation with regard to food-producing animals and hopes that current research in food-producing animal analgesics, such as Dr. Coetzee's, will provide much needed, validated methods for evaluation of pain, thereby encouraging the development and approval of analgesics for food-producing animals.

During the May 2008 International Symposium on Beef Cattle Welfare, organized by Dr. Coetzee, CVM encouraged drug sponsors to meet with them and discuss their proposed development plans for new food-producing animal analgesics. Discussions with CVM will facilitate analgesic drug approval for food-producing animals within the confines of the regulations under which CVM functions.

Due to the issues surrounding pain control in animals, CVM's Staff College recently invited Dr. Coetzee to speak about the hurdles facing researchers and the animal drug industry regarding development of analgesics for food-producing animals, particularly cattle.

There are two main categories of pain assessment—subjective (which introduces some of the observer's bias in scoring) and objective (these methods rely on biomarkers of pain, such as bloodwork values, which have little or no observer bias and are generally quantifiable).

Use of "subjective" methods to obtain data for pain studies generally relies on observations and scoring of visible physical signs of pain exhibited by cattle. Validated subjective methods of pain assessment (such as the Glasgow Short Form Pain Questionnaire for dogs, which can be obtained at *http://www.gla.ac.uk/faculties/vet/smallanimalhospital/ourservices/painmanagementandacupuncture/*) could be useful, particularly when they have clearly defined terms; however, none has been modified and validated for use in cattle. The observer's personal bias may still be introduced during scoring, thus, it is not uncommon to see differences in pain scores given by different observers for the same animal at the same time point.

Thus, researchers, including Dr. Coetzee, are trying to develop more objective tools for pain assessment. Examples of tools being evaluated by Dr. Coetzee's group include measurement of plasma Substance P values, evaluation of accelerometers, thermography, chute exit speed, and pressure mats.

Plasma Substance P: Substance P is a naturally occurring protein (neuropeptide) that plays roles in pain perception and transmission of nerve impulses, inflammation, regulation of various hormonal responses in the body, gastrointestinal movement, and vomiting.[16] Substance P helps regulate the excitability of the nerve cells associated with pain that are found in the dorsal horn of the spinal cord. Substance P is also involved in the integration of pain, stress, and anxiety.[17] Researchers have evaluated plasma Substance P levels in humans for varying conditions including osteoarthritis, headaches, and fibromyalgia.[18] They also found higher levels of plasma Substance P (27-times greater) in human patients with soft tissue injuries as compared to those from healthy control subjects.[19]

Based on these findings, Dr. Coetzee's group hypothesized that plasma Substance P response may be a more useful specific indicator of pain in cattle than plasma cortisol response. Cortisol is a hormone associated with the fight-or-flight system, and plasma levels of cortisol in animals are known to increase rapidly in the face of stressful but non-painful situations. Dr. Coetzee's group conducted a study evaluating plasma cortisol and plasma Substance P levels in 10 calves undergoing castration or simulated castration.[20] Average plasma cortisol concentrations in castrated calves were similar to those in uncastrated calves. Average plasma Substance P concentrations, however, were statistically significantly higher in castrated calves than those in uncastrated calves, lending support to their hypothesis. The group acknowledged that more research is necessary to distinguish how much of the plasma Substance P response after castration was due to stress from handling and how much was truly due to pain from the procedure. Overall, comparison of plasma Substance P and cortisol concentrations may provide a useful tool to help researchers, producers, and veterinarians distinguish pain from the stress of handling an animal for a given procedure.[21]

Accelerometers: Accelerometers are devices that can be used to measure an animal's movements in two or three dimensions. The devices are attached to an animal using leg bands. Behaviors such as standing, walking, grazing, or lying down, and the animal's posture can be recorded over a specified period of time and then analyzed. An advantage to using these devices is that animals on study can be used as their own controls—that is, baseline pre-procedure behavior for a given animal can be compared with its post-procedure behavior—thus reducing unexplained variability.

Dr. Coetzee's group conducted an accelerometer study in 12 calves, comparing calf activity changes pre- and post-castration with those of calves in a control (non-castrated) group.[22] Dr. Coetzee's group

(Continued, next page)

Pain Measurement Techniques . . . *(Continued)*

found that castrated calves spent proportionately more time standing after castration (82.2 percent), compared with their pre-castration readings (46.2 percent).[23] Castrated calves also spent less time eating compared to both their pre-castration readings and those of the control calves. The group recorded the calves' behavior during the study on video cameras and was able to corroborate the accelerometer data with the behavioral observations. In the future, accelerometers may prove to be useful tools with which to assess pain behavior in cattle.

Thermography: Thermography may provide researchers with a safe, hands-off way to evaluate cattle pain during studies. Thermography is based on measuring changes in surface body temperature in response to painful stimuli. A specialized camera is placed in a specific location and a set distance from an animal confined in a squeeze chute. The camera can then detect changes in skin temperature associated with blood flow to the skin (white = hot, green/blue = cool). Pain is thought to increase the levels of circulating norepinephrine and epinephrine "fight-or-flight" hormones in the body. Because the chemicals cause blood vessels to constrict, blood flow to the skin is decreased and the skin's temperature then decreases. Skin temperature changes, noted by the camera as changes in skin color, can be recorded and quantified, providing another objective source of data for pain assessment. In addition to being a safe way to evaluate cattle, another advantage, like accelerometers, is that animals being evaluated by thermography can be used as their own controls: pre- and post-procedure images can be compared for an individual animal.

Dr. Coetzee acknowledges that more research is needed to confirm the validity of using thermography for pain evaluation. Other areas in thermography Dr. Coetzee would like to evaluate include: comparing different areas of the body (for example, head versus chest) to see which provides the best thermography results, ensuring that an animal's plasma epinephrine levels correspond to its recorded thermography changes, and evaluating whether pain drugs would cause changes in thermography (less pain = less epinephrine = decreased skin temperature changes).[24]

Pressure Mats: Pressure mats, in addition to currently being evaluated in small animal medicine for pain evaluation, are also being evaluated for use in obtaining objective data for pain evaluation in cattle.[25] The mats contain built-in sensors that record pressure changes through all phases of an animal's stride. The data can be analyzed using special computer software to evaluate changes in duration and length of stride, force generated throughout a stride, the distribution of the force throughout a stride. The data give researchers a complete picture of how an animal is walking—how its weight is being distributed on each foot as it walks. The data are recorded as footprint images that vary in color depending on the amount of force an animal generates on each foot while walking (for example, red footprints mean the animal is putting a lot of pressure on those feet).

Dr. Coetzee's group has used video cameras to simultaneously record an animal as it walks across the pressure mats. The videos are then synchronized with the recorded pressure mat footfalls, giving the observers a way to score lameness for an animal subjectively (visual observations and scores) and objectively (numerical data points from pressure mats) at the same time. Again, this is a promising tool for use in future cattle pain studies.

Conclusion

Pain relief is a very hot topic in veterinary medicine. While there are currently no drugs specifically approved for analgesia in food-producing animals, there is growing interest in research in this area. The efforts of Dr. Coetzee and his fellow large-animal researchers around the world should ensure that pain measurement methods for food-producing animals are identified and that work toward the validation of these methods continues. Once validated pain measurement methods become available, they can then be used in the development and approval of much-needed analgesics for food-producing animals.

Endnotes

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[16] Ibid.

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[20] Ibid.

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Warning Letters *(Continued from page 4)*

Thus, food from both cows was adulterated within the meaning of the FFDCA.

Further investigation by FDA found that the animals are housed at this operation under inadequate conditions, whereby medicated animals with potentially harmful drug residues are likely to enter the food supply. Thus, food from these animals is adulterated within the meaning of the FFDCA.

The FDA investigation also found that sulfadimethoxine was used in an extralabel manner. The extralabel use of this drug in lactating dairy cows is prohibited by regulation. Further, the owner's extralabel use of sulfadimethoxine caused it to be unsafe and adulterated within the meaning of the FFDCA and resulted in an illegal drug residue.

WARNING LETTER TO: Alva Carter, Jr., and Allen Carter, co-owners, Carters Milk Factory: Portales, NM

Reason for Letter: Violative drug residues, improper extralabel drug use

Date: May 19, 2009

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm168471.htm

On or about July 7, 2008, the owners sold a cow for slaughter, which was later found by the USDA/FSIS to have violative residues of the drug flunixin in its liver tissue and the drug desfuroylceftiofur in its kidney tissue. Also, on or about August 13, 2008, the owners sold another cow for slaughter that was later found by the USDA/FSIS to have violative residues of flunixin in its liver tissue. Thus, food from both cows was adulterated within the meaning of the FFDCA.

Further investigation by FDA found that the animals are housed at this operation under inadequate conditions, whereby medicated animals with potentially harmful drug residues are likely to enter the food supply. Thus, food from these animals is adulterated within the meaning of the FFDCA.

The FDA investigation also found that flunixin meglumine and ceftiofur sodium were used in an extralabel manner. Use of both drugs in this manner caused them to be unsafe and adulterated within the meaning of the FFDCA. Further, the owners' extralabel use of flunixin meglumine resulted in an illegal drug residue.

WARNING LETTER TO: John Dollins, Tom Tune, and Tony Tune, co-owners, Opportunity Dairy: Clovis, NM

Reason for Letter: Violative drug residues

Date: May 28, 2009

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm168834.htm

(Continued, next page)

Warning Letters *(Continued)*

On May 12, 2008, the owners sold a cow for slaughter, which was later found by the USDA/FSIS to have violative residues of the drug flunixin in its liver and muscle tissues and the drug sulfadimethoxine in its liver tissue. The owners treated this cow with flunixin and sulfadimethoxine, but could not produce records to show the exact drugs used, how the drugs were administered, any extralabel use of the drugs, and how the meat withdrawal time was calculated. In addition, on July 7, 2008, the owner sold another cow for slaughter, which was later found by the USDA/FSIS to have violative residues of the drug desfuroylceftiofur in its kidney tissue. The owners treated this cow with desfuroylceftiofur, but could not produce any treatment records. Thus, food from both cows was adulterated within the meaning of the FFDCA.

Further FDA investigation found that the animals are housed at this operation under inadequate conditions, whereby medicated animals with potentially harmful drug residues are likely to enter the food supply. Thus, food from these animals is adulterated within the meaning of the FFDCA.

The FDA investigation also found that the owners violated the FFDCA by causing the adulteration of an animal that was sold and subsequently offered for sale to a slaughterhouse that ships in interstate commerce.

WARNING LETTER TO: Beau T. Boles, owner, Boles Livestock: Clovis, NM

Reason for Letter: Violative drug residues

Date: May 29, 2009

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm168597.htm

On or about the dates of May 13, 2008, July 8, 2008, and August 14, 2008, the owner sold a cow each day for slaughter. The cows were later found by the USDA/FSIS to have violative residues of the following drugs: flunixin (liver and muscle tissues), sulfadimethoxine (liver and muscle tissues), and desfuroylceftiofur (kidney tissue). Thus, food from these cows was adulterated within the meaning of the FFDCA.

Further FDA investigation found that the animals are housed at this operation under inadequate conditions, whereby medicated animals with potentially harmful drug residues are likely to enter the food supply. Thus, food from these animals is adulterated within the meaning of the FFDCA.

WARNING LETTER TO: Newton J. and Darlene A. Reynolds, co-owners, Newton Reynolds Farm: Alberg, VT

Reason for Letter: Violative drug residues, improper extralabel drug use

Date: May 29, 2009

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm172844.htm

On or about September 22, 2008, the owners sold a dairy cow for slaughter, which was later found by the USDA/FSIS to have violative residues of the drugs flunixin and oxytetracycline in its liver, kidney, and muscle tissues. Thus, food from this cow was adulterated within the meaning of the FFDCA.

Further investigation by FDA found that the animals are housed at this operation under inadequate conditions, whereby medicated animals with potentially harmful drug residues are likely to enter the food supply. Thus, food from these animals is adulterated within the meaning of the FFDCA.

The FDA investigation also found that flunixin and oxytetracycline were used in an extralabel manner and not under the supervision of a licensed veterinarian. Use of both drugs in this manner caused them to be unsafe and adulterated within the meaning of the FFDCA and resulted in illegal drug residues.

WARNING LETTER TO: Orlando Miguel, president, Pet Kiss, Inc.: Palmdale, CA

Reason for Letter: Marketing of unapproved new animal drug

Date: June 2, 2009

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm165062.htm

On June 2, 2009, the FDA sent Mr. Miguel a letter regarding his firm's illegal marketing of "Arthritis & Joint Formula" without an approved New Animal Drug Application (NADA). Mr. Miguel's Web site contained a testimonial statement and other statements indicating that his product is a new animal drug under the meaning of the FFDCA. Within the meaning of the FFDCA, FDA determined that Mr. Miguel's product is unsafe and adulterated, because it is not the subject of an approved NADA. In addition, Mr. Miguel violated the FFDCA by introducing an adulterated drug into interstate commerce.

(Continued, next page)

Warning Letters *(Continued)*

WARNING LETTER TO: Gilbert Hurtado, partner, G&H Dairy #1: Twin Falls, ID

Reason for Letter: Violative drug residues, improper extralabel drug use

Date: July 31, 2009

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm176800.htm

On or about December 1, 2008, Mr. Hurtado sold a dairy cow for slaughter, which was later found by the USDA/FSIS to have violative residues of the drug flunixin in its liver tissue. Thus, food from this cow was adulterated within the meaning of FFDCA.

Further investigation by FDA found that the animals are housed at this operation under inadequate conditions, whereby medicated animals with potentially harmful drug residues are likely to enter the food supply. Thus, food from these animals is adulterated within the meaning of the FFDCA.

The FDA investigation also found that Mr. Hurtado used flunixin in an extralabel manner and not under the supervision of a licensed veterinarian. Use of the drug in this manner caused it to be unsafe and adulterated within the meaning of the FFDCA and resulted in an illegal drug residue.

WARNING LETTER TO: Maurice Loehmer, president, MCAA Land & Cattle, LLC: Monterey, IN

Reason for Letter: Violative drug residues, improper extralabel drug use

Date: August 19, 2009

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm180922.htm

On or about August 9, 2008, Mr. Loehmer sold a dairy cow for slaughter, which was later found by the USDA/FSIS to have violative residues of the drug sulfadimethoxine in its liver tissue. Thus, the food from this cow was adulterated within the meaning of the FFDCA.

Further investigation by FDA found that the animals are housed at this operation under inadequate conditions, whereby medicated animals with potentially harmful drug residues are likely to enter the food supply. Thus, food from these animals is adulterated within the meaning of the FFDCA.

The FDA investigation also found that Mr. Loehmer used sulfadimethoxine in an extralabel manner and not under the supervision of a licensed veterinarian. Use of the drug in this manner caused it to be unsafe and adulterated within the meaning of the FFDCA and resulted in an illegal drug residue.

WARNING LETTER TO: Jerry and Linda Korle, owners, J&L Dairy: Clarissa, MN

Reason for Letter: Violative drug residues, improper extralabel drug use

Date: August 28, 2009

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm181496.htm

On or about March 19, 2008, the owners sold a dairy cow for slaughter, which was later found by the USDA/FSIS to have violative residues of the drug procaine G penicillin in its liver tissue. Thus, food from this cow was adulterated within the meaning of FFDCA.

Further investigation by FDA found that the animals are housed at this operation under inadequate conditions, whereby medicated animals with potentially harmful drug residues are likely to enter the food supply. Thus, food from these animals is adulterated within the meaning of the FFDCA.

The FDA investigation also found that the owners used procaine G penicillin in an extralabel manner and not under the supervision of a licensed veterinarian. Use of the drug in this manner caused it to be unsafe and adulterated within the meaning of the FFDCA and resulted in an illegal drug residue.

WARNING LETTER TO: Roger E. Snyder, co-owner and manager, H.G. Early-Snyder Family Farm, LLC: Lexington, KY

Reason for Letter: Violative drug residues

Date: August 28, 2009

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm181092.htm

On or about October 29, 2008, Mr. Snyder sold a bull at auction, which then entered interstate commerce. After slaughter, the bull was found by the USDA/FSIS to have violative residues of the drug phenylbutazone in its kidney tissue. There is no FDA-established tolerance for residues of phenylbutazone in food from cattle. Thus, food from this bull was adulterated within the meaning of the FFDCA.

Further investigation by FDA found that the animals are housed at this operation under inadequate conditions, whereby medicated animals with potentially harmful drug residues are likely to enter the food supply. Thus, food from these animals is adulterated within the meaning of the FFDCA.

Approvals for March – August 2009

CVM has published in the *Federal Register* notice of the approval of these Original New Animal Drug Applications (NADAs)

- AVIAX II (semduramicin sodium biomass) and STAFAC (virginiamycin) (NADA 141-289), filed by Phibro Animal Health. The single-ingredient Type A medicated articles are used to make two-way combination drug Type C medicated feeds for broiler chickens. The application provides for use of the drugs in Type C medicated feeds. Notice of the approval was published August 18, 2009.
- AVATEC (lasalocid sodium) and 3-NITRO (roxarsone) (NADA 141-293), filed by Alpharma, Inc. The single-ingredient Type A medicated feed articles are used to make two-way combination drug Type C medicated feeds for use in growing turkeys. The application also removes an incorrect human food safety warning and revises an animal safety limitation for use of roxarsone in chicken and turkey feeds. Notice of the approval was published July 15, 2009.
- VETORYL (trilostane) Capsules (NADA 141-291), filed by Dechra, Ltd. The application provides for veterinary prescription use of VETORYL Capsules in dogs for treatment of pituitary dependent hyperadrenocorticism and for treatment of hyperadrenocorticism due to adrenocortical tumor. Notice of the approval was published May 11, 2009.
- FELIMAZOLE (methimazole) Coated Tablets (NADA 141-292), filed by Dechra, Ltd. The NADA provides for veterinary prescription use of FELMIAZOLE Coated Tablets in cats for the treatment of hyperthyroidism. Notice of the approval was published June 11, 2009. (See *FDA Approves First Drug to Treat Hyperthyroidism in Cats* on page 2.)
- PALLADIA (toceranib phosphate) Tablets (NADA 141-295), filed by Pharmacia & Upjohn Co. The NADA provides for veterinary prescription use of PALLADIA Tablets in dogs for the treatment of Patnaik Grade II or III, recurrent, cutaneous mast cell tumors with or without regional lymph node involvement. Notice of the approval was published June 18, 2009. (See *FDA Approves Drug to Treat Cancer in Dogs* on page 3.)

CVM has published in the *Federal Register* notice of the approval of these Supplemental New Animal Drug Applications (NADAs)

- CHLORMAX (chlortetracycline), filed by Alpharma, Inc. (supplement to NADA 046-699). The supplement provides for revised Blue Bird labeling for chlortetracycline Type A medicated articles used to formulate Type B and Type C medicated feeds in various classes of livestock and poultry. Notice of the approval was published June 12, 2009.
- SEVOFLO (sevoflurane) (supplement to NADA 141-103), filed by Abbott Laboratories. SEVOFLO is used for induction and maintenance of general anesthesia in dogs. The supplement provides for a revised induction dose. Notice of the approval was published March 11, 2009.
- TYLAN (tylosin) Injection (supplement to NADA 012-965), filed by Elanco Animal Health. TYLAN is an injectable solution used for the treatment of animal diseases associated with several bacterial pathogens. The supplement provides for changing a bovine pathogen name on product labeling. Notice of the approval was published March 19, 2009.
- PANACUR (fenbendazole), filed by Intervet, Inc. (supplement to NADA 104-494). The supplement provides for a revised human food safety warning on product labeling. Notice of the approval was published April 17, 2009.
- NEO-OXY 50/50, NEO-OXY 100/100, and NEO-OXY 100/100 MR (neomycin and oxytetracycline) (supplement to NADA 138-939), filed by Pennfield Oil Co. The supplement provides for revised labeling of these products to comply with effectiveness findings under the DESI (Drug Efficacy Study Implementation) program. The products are two-way, fixed-combination Type A medicated articles used to make two-way combination drug Type B and Type C medicated feeds containing oxytetracycline and neomycin sulfate, in a 1:1 ratio, for several production and therapeutic indications in chickens, turkeys, swine, cattle, and sheep. Notice of the approval was published August 13, 2009.
- REVOLUTION (selamectin) (supplement to NADA 141-152), filed by Pfizer, Inc. The supplement increases the minimum age of treatment to 8 weeks (previously 6 weeks) for kittens treated with the topical selamectin solution. Notice of the approval was published April 30, 2009.
- VETORYL (trilostane) Capsules (supplement to NADA 141-291), filed by Dechra, Ltd. The supplement provides for use of a 10-milligram capsule size. Notice of the approval was published June 26, 2009.

(Continued, next page)

Approvals for March – August 2009 *(Continued)*

CVM has published in the *Federal Register* notice of the approval of these Abbreviated New Animal Drug Applications (ANADAs)

- GB (gentomicin sulfate and betamethasone valerate) Topical Spray (ANADA 200-388), filed by American Pharmaceuticals and Cosmetics, Inc. The ANADA provides for veterinary prescription use of GB Topical Spray in dogs. The product is approved as a generic copy of Schering-Plough Animal Health Corporation's GENTOCIN Topical Spray, under NADA 132-388. Notice of the ANADA approval was published May 15, 2009.

- Amprolium 9.6% Oral Solution (ANADA 200-463), filed by IVX Animal Health, Inc. The ANADA provides for the use of generic amprolium concentrate solution to make medicated drinking water for chickens and turkeys for the treatment of coccidiosis. The product is a generic copy of Huvepharma, AD's AMPROVINE 9.6% Solution, approved under NADA 13-149. Notice of the ANADA approval was published March 11, 2009.

- Ceftiofur Sodium Sterile Powder (ANADA 200-420), filed by Cephazone Pharma, LLC. The ANADA provides for the use of Ceftiofur Sodium Sterile Powder as an injectable solution in dogs, horses, cattle, swine, day-old chickens, turkey poults, sheep, and goats as therapy for various bacterial infections. The product is a generic copy of Pharmacia & Upjohn Co.'s NAXCEL (ceftiofur sodium) Sterile Powder for Injection, approved under NADA 140-338. Notice of the ANADA approval was published July 15, 2009.

- Nitrofurazone Soluble Dressing (ANADA 200-425), filed by First Priority, Inc. The ANADA provides for use of Nitrofurazone Soluble Dressing in horses for prevention or treatment of superficial bacterial infections of wounds, burns, and cutaneous ulcers. The product is a generic copy of Squire Laboratories, Inc.'s FURA-ZONE (nitrofurazone) ointment, approved under NADA 132-427. Notice of the ANADA approval was published August 3, 2009.

- Flunixin Injection –S (ANADA 200-476), filed by Norbrook Laboratories, Ltd. The ANADA provides for use of Flunixin Injection –S in swine for various bacterial infections. The product is a generic copy of Schering-Plough Animal Health's BANAMINE-S (flunixin meglumine) Injectable Solution, approved under NADA 101-479. Notice of the ANADA approval was published July 15, 2009.

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